REMARKS

Status of the claims

Claims 1, 6, and 25-37 are hereby amended merely for clarity and to maintain proper antecedent basis, and new claims 38-45 have been added. No new matter is introduced by this amendment. Entry of this amendment is respectfully requested.

As such, claims 1, 6, and 25-45 are presently pending.

A current claim listing is presented above with status identifiers for each claim, in accordance with 37 C.F.R. §1.121(c).

Withdrawn Rejections

The Examiner stated that the previous 103 rejection and new matter rejection have each been withdrawn (page 2 of the January 29, 2008 Office Action).

Rejection under 35 USC §112, first paragraph, enablement

Claims 1, 6, and 25-37 stand rejected under 35 USC §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In maintaining this rejection, the Examiner stated that the post-filing publication (Luke et al., *Arterioscler. Thromb. Vasc. Biol.* 2007 ;27 :2030-2036) submitted in Applicant's response of October 30, 2007 is not acceptable absent presentation in declaration form. The Examiner also stated that Luke et al. teaches the LPA I4399M SNP (rs3798220) is associated with severe coronary artery disease (CAD), and the instant claims are drawn to coronary stenosis, and the Examiner requested Applicants to discuss the relationship between CAD and coronary stenosis. The Examiner also stated that the response does not address the heterozygosity issue, such as if a person is a heterozygote with a GA genotype, it is allegedly unclear how the person may be at both an increased and a decreased risk for coronary stenosis.

In response, Applicants respectfully assert that the post-filing publication of Luke et al. (*Arterioscler. Thromb. Vasc. Biol.* 2007 ;27 :2030-2036) that was previously submitted in Applicant's response of October 30, 2007 should be considered by the Patent Office even if not

in declaration form since MPEP 716.02(g) provides that "Publications may, however, be evidence of the facts in issue and should be considered to the extent that they are probative".

However, in the interest of expediting prosecution, the post-filing publication of Luke et al. is hereby re-submitted in a Rule 132 declaration (as Exhibit A attached to the Rule 132 declaration; additionally, the online supplement which accompanies Luke et al. is provided as Exhibit B).

With respect to the Examiner's request to discuss the relationship between coronary artery disease (CAD) and coronary stenosis, Applicants submit that these terms are used synonymously in the Luke et al. publication (as also discussed in the attached Rule 132 declaration at the fourth point). In the Luke et al. publication, CAD is defined based only on coronary stenosis, and the severity of CAD is defined by the degree of coronary stenosis. For example, as stated in Luke et al., "The severity of CAD was defined by a stenosis score..." (p. 2031, column 1, 1st sentence). Furthermore, Luke et al. also stated that "Severe coronary artery disease (CAD), characterized by occlusive epicardial coronary stenosis..." (p. 2030, column 1, 1st sentence) and "The first goal was to compare cases and controls at the extreme ends of the stenosis phenotype..." (p. 2031, column 1, 1st paragraph of "Study Subjects" section). Thus, it is clear in the Luke et al. publication that CAD was defined based only on coronary stenosis and, accordingly, these terms are used synonymously in the Luke et al. publication.

It should be also noted that "coronary artery disease" can also be interpreted in the art as being broader than "coronary stenosis". For example, coronary artery disease may also be interpreted as including angina, etc. However, in the specific instance of the Luke et al. publication, "coronary artery disease" is clearly defined based only on coronary stenosis and therefore, the terms "coronary artery disease" and "coronary stenosis" are synonymous with respect to interpreting the Luke et al. publication in relationship to corroborating the enablement of the claims currently under examination.

Consequently, the Luke et al. publication corroborates the instant patent specification and provides further support for the enablement of the claimed invention. For example, the Luke et al. publication demonstrates that the instantly claimed SNP (referred to as LPA I4399M (rs3798220) in the publication) has been associated with severe CAD/coronary stenosis in three independent studies (see, e.g., Table 2 and Table 3 of Luke et al.). The studies conducted in the

published article used genotype information from genotyping the patients individually to confirm the pooled studies described in the Examples section of the instant patent specification.

With respect to heterozygous individuals, Applicants submit that heterozygotes (i.e., individuals with the GA genotype, or the complementary genotype) have an increased risk for coronary stenosis as compared to individuals with the AA genotype. As shown in the Luke et al. publication (provided in the attached Rule 132 declaration), carriers (either *heterozygous* or homozygous) of the G allele are associated with an increased risk for coronary stenosis as compared to noncarriers of the G allele (i.e., homozygous carriers of the A allele or the reference group). The alleles at this SNP correspond as follows: the G nucleotide corresponds to the methionine (M) amino acid, and the A nucleotide corresponds to the isoleucine (I) amino acid (as indicated in Table 1 of the instant application as well as in Table 2 of Luke et al., for example).

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 USC §112, first paragraph, for alleged lack of enablement.

Conclusions

In conclusion, in view of the above remarks and the attached Rule 132 declaration, Applicants submit that the present application is fully in condition for allowance.

The Examiner is invited to contact the undersigned via telephone if a phone interview would expedite the prosecution of the instant patent application.

Respectfully submitted,

By: _____
Justin D. Karjala, Reg. No.: 43,704

Date: May 29, 2008

Celera
1401 Harbor Bay Parkway
Alameda, CA 94502
Tel: 510-749-4224
Fax: 510-749-4266

Attachment: Rule 132 declaration (with Exhibit A and Exhibit B)

US: 10/796,280
Atty. Docket: CL1510ORD

Certificate of Transmission
I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office, Fax Number 571-273-8300 on May 29, 2008 by _____.
Joel S. White

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Cargill, et al.

Art Unit: 1634

Serial No.: 10/796,280

Examiner: Jeanine A. Goldberg

Filed: March 10, 2004

Attorney Docket No.: CL1510ORD

For: GENETIC POLYMORPHISMS ASSOCIATED WITH STENOSIS, METHODS OF DETECTION AND USES THEREOF

Declaration under 37 C.F.R. §1.132

DECLARATION OF MAY M. LUKE UNDER 37 C.F.R. §1.132

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, MAY M. LUKE, do declare that:

1. I am a co-inventor of the invention described and claimed in the above-identified patent application.

2. I currently hold the position of Manager, Cardiovascular Disease at Celera (Alameda, California), which is a business unit of Applera Corporation (the assignee of the above-identified application), where I have been employed since September 2001. I received the degree of Doctor of Philosophy in Molecular Pharmacology from the State University of New York at Stony Brook in 1990.

3. I conducted experiments to identify genetic variants associated with severe coronary artery disease (CAD). The methods, results, and discussion of the experiments have been published in May M. Luke *et al.*, "A polymorphism in the protease-like domain of apolipoprotein(a) is associated with severe coronary artery disease", *Arterioscler Thromb Vasc*

Biol. 2007 Sep;27(9):2030-6, a copy of which is attached herewith as Exhibit A (referred to herein as the "Exhibit A publication"), and in an online supplement that accompanies the above-cited May M. Luke *et al.* publication, a copy of which is attached herewith as Exhibit B (referred to herein as the "Exhibit B online supplement").

4. In the Exhibit A publication, the severity of coronary artery disease (CAD) is defined by a stenosis score, and thus the definition of coronary artery disease in the Exhibit A publication was based exclusively on coronary stenosis. Therefore, the terms "coronary artery disease" and "coronary stenosis" are used synonymously in the Exhibit A publication.

5. The SNP referred to as rs3798220 or I4399M in the Exhibit A publication is the same as the SNP represented by position 101 of SEQ ID NO:19350 in the above-identified patent application and which is also referred to as hCV25930271. The alleles at this SNP correspond as follows: the guanine (G) nucleotide corresponds to the methionine (M) amino acid, and the adenine (A) nucleotide corresponds to the isoleucine (I) amino acid.

6. Using the methods described in the Exhibit A publication and in the Exhibit B online supplement, SNP rs3798220 was found to be significantly associated with severe CAD in three independent case-control studies (clinical characteristics of cases and controls in each of the three studies is provided in Table 1 in the Exhibit A publication), as follows:

- In Study 1, the M allele of SNP rs3798220 had an allelic odds ratio for severe CAD of 3.79 (95% confidence interval 1.97-7.29) with a p-value of <0.001 (as shown in Table 2 in the Exhibit A publication).

- In Study 2, the M allele of SNP rs3798220 had an allelic odds ratio for severe CAD of 2.25 (90% confidence interval 1.27-3.97) with a p-value of 0.010 (as shown in Table 2 in the Exhibit A publication).

- In Study 3, the IM genotype of SNP rs3798220 had an unadjusted odds ratio for severe CAD of 1.94 (90% confidence interval 1.05-3.59) with a p-value of 0.039, and the MM and IM genotypes combined had an unadjusted odds ratio for severe CAD of 2.01 (90% confidence interval 1.09-3.70) with a p-value of 0.031 (the II genotype was the reference, with odds ratio of 1.00) (as shown in Table 3 in the Exhibit A publication).

- Also in Study 3, when adjusted for age, sex, smoking, diabetes, dyslipidemia, hypertension, and BMI, the IM genotype of SNP rs3798220 had an adjusted odds ratio for severe CAD of 3.09 (90% confidence interval 1.48-6.48) with a p-value of 0.006, whereas the MM and IM genotypes combined had an adjusted odds ratio for severe CAD of 3.14 (90% confidence interval 1.51-6.56) with a p-value of 0.005 (the II genotype was the reference, with odds ratio of 1.00) (as shown in Table 3 in the Exhibit A publication).

7. In conclusion, because SNP rs3798220 was found to be significantly associated with CAD in three independent case-control studies as described in the Exhibit A publication, and because CAD is synonymous with coronary stenosis as used in the Exhibit A publication, the Exhibit A publication therefore provides further evidence of the significance and consistency of the association of SNP rs3798220 with coronary stenosis.

8. I declare further that all statements made in this declaration are of my own knowledge and are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 5-29-08

MAY M. LUKE